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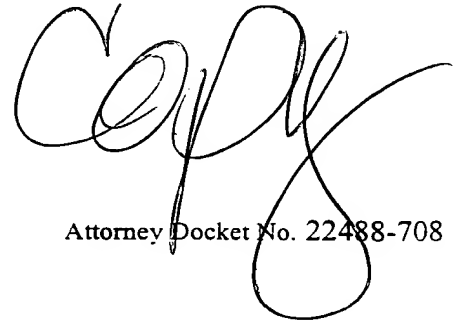
533 Rec'd PCT/PTO 14 JUL 2000

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Attorney Docket No. 22488-708

**IN THE INTERNATIONAL BUREAU  
OF THE WORLD INTELLECTUAL PROPERTY ORGANIZATION**

In re Patent Application of ) PATENT APPLICATION  
)  
Medical University of South Carolina )  
Foundation for Research Development )  
)  
Application No.: PCT/US99/26221 )  
)  
Filed: 05 November, 1999 )  
)  
Title: A Method for Treating Tumors Using Fas-) Induced Apoptosis )  
\_\_\_\_\_ )

**AMENDMENT OF THE CLAIMS UNDER ARTICLE 19**

The International Bureau  
World Intellectual Property Organization  
34, chemin des Colombettes  
1211 Geneva 20  
SWITZERLAND

Dear Sir or Madam:

Responsive to the *Notification of Transmittal of the International Search Report or the Declaration* mailed, 4 May 2000, the Applicant files this *Amendment of the Claims Under Article 19* and respectfully requests inclusion of the following amendment under Article 19 in the published PCT patent application.

09600521-092701

## AMENDMENTS

Please cancel claims 1-46.

Please add the following new claims.

1. A method for inducing death in cells that express an apoptosis-mediating receptor, the method comprising:

introducing an expression vector into a group of cells comprising cells that express an apoptosis-mediating receptor, the expression vector comprising a polynucleotide sequence encoding an apoptosis-signaling ligand whose expression is regulated by a conditional promoter in the vector, the cells into which the expression vector is introduced expressing the apoptosis-signaling ligand when conditions are suitable to activate the conditional promoter, the expressed apoptosis-signaling ligand inducing cell death in those cells which express the apoptosis-mediating receptor through interaction between the apoptosis-signaling ligand and the apoptosis-mediating receptor.

2. The method of claim 1, wherein the apoptosis-mediating receptor is a membrane-bound receptor.
3. The method of claim 2, wherein the membrane-bound receptor is Fas.
4. The method of claim 3, wherein the apoptosis-signaling ligand is capable of binding to Fas.
5. The method of claim 4, wherein the apoptosis-signaling ligand is an antibody that is capable of binding to Fas and signals Fas-mediated apoptosis in cells expressing Fas.
6. The method of claim 4, wherein the apoptosis-signaling ligand is a membrane protein.
7. The method of claim 6, wherein the membrane protein is FasL.

8. The method of claim 3, wherein the group of cells into which the expression vector is introduced comprises a mixture of cells which express Fas and cells which do not express Fas.

9. The method of claim 3, wherein the expression vector is introduced into cells which do not express Fas.

10. The method of claim 3, wherein the expression vector is introduced into cells which do express Fas.

11. The method of claim 3, wherein the expression vector is introduced into cells which do not express Fas and cells which do express Fas.

12. The method of claim 1, wherein the group of cells are contained in a solid tumor.

13. The method of claim 12, wherein the solid tumor is selected from the group consisting of breast, prostate, brain, bladder, pancreas, rectum, parathyroid, thyroid, adrenal, head and neck, colon, stomach, bronchi and kidney tumors.

14. The method of claim 1, wherein introducing an expression vector into the group of cells is performed parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form.

15. The method of claim 1, wherein introducing the expression vector is performed by direct injection of the expression vector among the group of cells.

16. The method of claim 1, wherein the expression vector is a plasmid.

17. The method of claim 1, wherein the expression vector is a viral vector.
18. The method of claim 17, wherein the viral vector is selected from the group consisting of adenovirus, adeno-associated virus, vaccinia, retrovirus, and herpes simplex virus vectors.
19. The method of claim 17, wherein the expression vector is an adenoviral vector.
20. The method of claim 1, wherein the conditional promoter is a tissue-specific promoter.
21. The method of claim 20, wherein the tissue-specific promoter is selected from the group consisting of a prostate-specific promoter, a breast-specific promoter, a pancreas-specific promoter, a colon-specific promoter, a brain-specific promoter, a kidney-specific promoter, a bladder-specific promoter, a lung-specific promoter, a liver-specific promoter, a thyroid-specific promoter, a stomach-specific promoter, an ovary-specific promoter, and a cervix-specific promoter.
22. The method of claim 1, wherein the group of cells are prostate cancer cells and the conditional promoter of the expression vector is a prostate-specific promoter.
23. The method of claim 22, wherein the prostate-specific promoter is selected from the group consisting of PSA,  $\Delta$ PSA, ARR2PB, and PB promoters.
24. The method of claim 1, wherein the conditional promoter is an inducible promoter.
25. The method of claim 24, wherein the inducible promoter is a promoter inducible by tetracycline or doxycycline.
26. The method of claim 24, wherein the inducible promoter is a promoter inducible by steroid.

27. The method of claim 26, wherein the steroid is selected from the group consisting of glucocorticoid, estrogen, androgen, and progesterone.
28. The method of claim 1, the method further comprising creating the conditions suitable to activate the conditional promoter.
29. The method of claim 28, wherein creating the conditions suitable to activate the conditional promoter comprises delivering to the group of cells tetracycline or deoxycycline.
30. The method of claim 28, wherein creating the conditions suitable to activate the conditional promoter comprises delivering to the group of cells a steroid selected from the group consisting of glucocorticoid, estrogen, androgen, and progesterone .
31. The method of claim 1, wherein the expression vector further comprises a reporter gene.
32. The method of claim 31, wherein the expression vector expresses the reporter gene as a fusion protein with the apoptosis-signaling ligand.
33. The method of claim 32, wherein the reporter gene encodes green fluorescent protein.
34. The method of claim 1, wherein the expression vector further comprises a polynucleotide sequence encoding a regulatory protein.
35. The method of claim 34, wherein the expression vector expresses the regulatory protein as a fusion protein with the apoptosis-signaling ligand.
36. The method of claim 35, wherein the regulatory protein in the fusion protein is a protein that causes tissue-specific localization of the apoptosis-signaling ligand.

37. The method of claim 1, wherein the method is performed *ex vivo* where the group of cells into which the expression vector is introduced are contained in a sample taken from a patient having cancer.

38. The method of claim 1, wherein the method is performed *in vitro* where the group of cells into which the expression vector is introduced are contained in a cell culture.

39. The method of claim 1, wherein the apoptosis-signaling ligand is selected from the group consisting of Bax, Bad, Bak, and Bik.

40. An adenoviral expression vector comprising:  
a conditional promoter, and  
a polynucleotide sequence encoding a membrane-bound ligand whose expression is regulated by the conditional promoter in the vector, the ligand signaling apoptosis in cells that express an apoptosis-mediating receptor.

41. The vector of claim 40, wherein the membrane-bound ligand is capable of binding to Fas.

42. The method of claim 41, wherein the membrane-bound ligand is FasL.

43. The vector of claim 40, wherein the conditional promoter is a tissue-specific promoter.

44. The vector of claim 43, wherein the tissue-specific promoter is selected from the group consisting of a prostate-specific promoter, a breast-specific promoter, a pancreas-specific promoter, a colon-specific promoter, a brain-specific promoter, a kidney-specific promoter, a bladder-specific promoter, a lung-specific promoter, a liver-specific promoter, a thyroid-specific promoter, a stomach-specific promoter, an ovary-specific promoter, and a cervix-specific promoter.

45. The vector of claim 43, wherein the tissue-specific promoter is a prostate-specific promoter.
46. The vector of claim 45, wherein the prostate-specific promoter is selected from the group consisting of PSA,  $\Delta$ PSA, ARR2PB, and PB promoters.
47. The vector of claim 40, wherein the conditional promoter is an inducible promoter.
48. The vector of claim 47, wherein the inducible promoter is a promoter inducible by tetracycline or doxycycline.
49. The vector of claim 47, wherein the inducible promoter is a promoter inducible by steroid.
50. The method of claim 49, wherein the steroid is selected from the group consisting of glucocorticoid, estrogen, androgen, and progesterone.
51. An adenoviral expression vector comprising:  
a tetracycline-responsive element;  
a polynucleotide sequence encoding a transactivator protein which is capable of binding to the tetracycline-responsive element; and  
a polynucleotide sequence encoding a target protein whose expression is regulated by the binding of the transactivator protein to the tetracycline-responsive element.
52. The vector of claim 51, wherein the tetracycline-responsive element and the polynucleotide sequence encoding the transactivator protein are positioned at opposite ends of the adenoviral vector.
53. The vector of claim 52, wherein the tetracycline-responsive element is positioned in the E4 region of the adenoviral vector and the polynucleotide sequence encoding the transactivator protein is positioned in the E1 of the adenoviral vector.

54. The vector of claim 51, wherein the adenoviral vector does not include the E3 region of adenovirus.
55. The vector of claim 51, wherein the adenoviral vector does not include the E4 region of adenovirus except for the Orf6 of the E4 region.
56. The vector of claim 51, wherein the expression of the target protein is repressed in the presence of tetracycline or doxycycline.
57. The vector of claim 51, wherein expression of the target protein is activated in the presence of doxycycline.
58. The vector of claim 51, wherein the target protein is a Fas ligand.
59. The vector of claim 51, wherein the viral expression vector further comprises a polynucleotide sequence encoding a reporter protein.
60. The vector of claim 59, wherein the reporter protein and the target protein are encoded as a fusion protein.
61. The vector of claim 59, wherein the reporter protein is a green fluorescent protein.
62. The vector of claim 51, wherein the adenoviral expression vector further comprises a polynucleotide sequence encoding a regulatory protein.
63. The vector of claim 62, wherein the regulatory protein and the target protein are encoded as a fusion protein.
64. The vector of claim 63, wherein the regulatory protein in the fusion protein is a protein that causes tissue-specific localization of the target protein.



65. An adenoviral vector that is pAd<sub>TET</sub>.

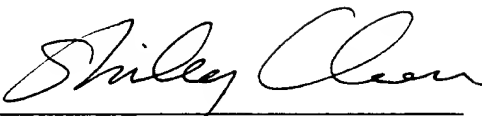
66. An adenoviral vector that is Ad/FasL-GFP<sub>TET</sub>.

Support for independent claim 1 appears on page 9, lines 4-11.

Enclosed are substitute pages 44 through 48 of the claims.

Respectfully submitted,

Dated: June 30, 2000

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